"Bazaar's" Liz Tilberis

Ovarian Cancer: One Woman's Fight.

Fertility drugs in her late 20s. Ovarian cancer in her early 40s. If there is a link, Bazaar's editor in chief wants others to know.

By Aimee Lee Ball

Gallows humor: We are joking about "the Cancer Diet." She works in fashion, where overweight is akin to ax-murdering, and when she left her native Britain several years ago for a great job in New York, the arrival of her size-14 figure was greeted by rude gossip. Now she's lost almost 30 pounds, a delicate shadow of her former self. Nine weeks of chemotherapy did what Jenny Craig never could. Last week was the first time she could make dinner for her children without throwing up.

It started with a missed OB-GYN appointment, just a routine feet-in-the-stirrups, undignified probing of the privates that she put off for a year. (Too busy—new job, new city, new country.) But she felt vaguely lousy all last fall, and when she finally went for a checkup in December, her stomach was bloated. The doctor noted on her file that she'd had unsuccessful treatment with the fertility drugs Clomid and Pergonal in the late 1970s and ultimately adopted two children. She was immediately referred to an oncologist, and within two weeks she was having surgery for ovarian cancer, stage three. At stage four they tell you to go home and get your affairs in order.

This woman is dismayed and frustrated that she was never told of an infertility drug–cancer link, that she never had a chance to evaluate the risk/benefit ratio or, after choosing treatment, to have vigilant screening. She is determined that other women be better informed, and she has the podium to carry out her mandate: This woman is Elizabeth Tilberis, editor in chief of *Harper's Bazaar.*

The statistics are stunning: Nearly 60 percent of ovarian-cancer cases are fatal because three-quarters of the women diagnosed already have advanced disease. It's a silent killer. The ovaries sit in a rather commodious abdominal cavity that can accommodate a lot of disease, undetected until it's too late. The symptoms are subtle and, because this cancer hits so many women around the time of menopause, too often dismissed as a natural part of aging. The telltale tummy bulge is attributed to "middle-age spread," and "early satiety"—feeling full after a small meal—is blamed on sluggish appetite. It doesn't cause bleeding in postmenopausal women or a change in the periods of younger, menstruating women. "Both patients and physicians delay," says Peter R. Dottino, M.D., director of gynecologic oncology at Mount Sinai Medical Center in New York, who treated Tilberis. "If somebody comes into the office with these nonspecific complaints, how far do I pursue it? What's my index of suspicion in taking care of patients? It's a tough, tough problem."

As with other health crises, it took the death of a celebrity—in this case, Gilda Radner, in 1989—to sensitize the public and increase awareness. But Radner was one of fewer than five percent of ovarian-cancer patients with a family history of the disease. There is an enormous impetus for the other cases, the overwhelming majority, to be detected early, when there is a salubrious cure rate (at least 80 percent five-year survival for stage-one diagnosis). But there is no routine screening technique, like the mammogram for breast cancer and the Pap smear for cervical cancer, that is recommended and endorsed for widespread use.

If you are breathing hard, know this: Ovarian cancer is rare, particularly for women under the age of 40. (Dramatizing it for a character on *thirtysomething* was a statistical oddity.) The American Cancer Society predicts about 24,000 new cases diagnosed in 1994 in this country, or a risk of about 1 in 70 for an American woman in her lifetime. Compare that to 180,000 cases of breast cancer—the well-quoted 1 in 9 women. Colon cancer kills more women than all the gynecological cancers put together. (Yes, colon cancer, which is probably the last thing you worry about.) And—yoo-hoo, smokers—the leading cause of cancer death for women is lung cancer.

Ovarian cancer defies detection during a routine pelvic exam because what feels normal to even experienced hands rummaging in our nether lands is so subjective. "The functioning ovary is in the business of varying its size and of making cysts every month," explains Carmel J. Cohen, M.D., director of gynecologic services at Mount Sinai Medical Center. "It is through those cysts that ovulation occurs. The follicle surrounding the egg enlarges and ruptures near the surface of the ovary, and the egg is extruded along with some supportive fluids. That cycle should occur monthly in menstruating women until the time of menopause." All kinds of things have been implicated in causing ovarian cancer (including the use of talc), but the common thesis holds that the disease is an offshoot of ovulation gone awry, that in the normal repair of that monthly rupture, cells must divide, and some cells run amok. Women who take a break from ovulation—say, by having a couple of babies or by taking oral contraceptives—are doing less frequent damage to their ovaries and are at a lower risk for the disease.

Since the ovaries shrink after menopause, it has also been suggested that a palpable ovary in an older woman is an alarm bell, but Cohen considers it a primitive method, dependent on the average doctor's capacity to discriminate between an almond and a pecan simply by feel: "The postmenopausal ovary is about the size of an almond," he explains. "If there's a cancer, it's the size of a pecan, but then there are already a billion cancer cells present." The situation is complicated when the woman is, like the average American, more zaftig than sylph. "Think about it this way," says Cohen. "On a mattress you place a pecan. On top of the pecan, you put sheets and a thin blanket. If you run your hands on the top, it is probable you will feel the pecan. Now put a quilt and a bedspread on, and think about the probability of feeling the pecan. If you throw a grapefruit under there, you'll feel it, but by the time things are grapefruit-size they're going to be out of hand." It's obvious why early detection is vital. But our only choices are two hotly debated possibilities, a blood test and a sonogram.

A tumor is a foreign body, and a blood test called CA 125 measures a protein that is produced by the cancer and shed into the bloodstream. We know that 80 percent of women with ovarian cancer have an elevated amount of this protein (over 35 units per milliliter). But CA 125 can be raised by many other benign conditions: menstruation, pregnancy, fibroids, cysts, endometriosis, pelvic inflammatory disease—anything that irritates the abdominal cavity. *Men* can have an elevated CA 125. Because of the many false positives, the test alone is considered an inefficient tool for diagnosis, with a huge potential to send a woman off on a merry-go-round of further evaluation that could end in the operating room. "Once you have an elevated test, there's nothing I can do to convince you that you

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ardy 20 years down the pike? "It's a disturbing possibility," says Sharon B. Diamond, M.D., the gynecologist who attended Liz Tilberis. "Many women feel very desperate when they go for infertility treatment and may not be in a position to evaluate the risk." Peter Dottino also has more questions than answers for infertile women. "How crazed should you be if you've been exposed to those drugs?" he asks rhetorically. "How radical? Should you have your ovaries out? That's the far-case scenario." Such a procedure, called prophylactic ovariectomy, is a draconian solution, and not even foolproof. There are known cases, undisputed in the scientific literature, of women getting ovarian cancer after their apparently healthy ovaries were removed. Pathologists can look at a slide of cancerous tissue to tell the site of origin, and these were cancers of organs that weren't even there. There's an explanation, of course: Cancer developed in the peritoneum, the abdominal lining surrounding the ovaries. "Some people think that ovarian cancer is really more of a cancer of the peritoneum," explains Dottino, "which gets trapped inside the ovary to cause the cancer."

Five years ago Ceil Sinnex had prophylactic surgery after losing her grandmother, aunt, and two cousins to ovarian cancer. She went on to establish the Ovarian Cancer Prevention & Early Detection Foundation, a grassroots group that disseminates information and provides research grants. Sinnex believes that the lack of clout and public awareness have relegated the disease to a position of ignored stepchild in the scientific community. "Ovarian cancer is so lethal and so disgracefully neglected that it is a modern curse," she says. "There is no early-detection test because no relatively serious funding commitment has ever been made to find one. Spokesmen for the status quo are now using the term 'emotional trauma' as a reason to slam shut the door on existing detection procedures. I agree that it is very disturbing when a woman receives an elevated CA 125 result. Is it less disturbing when she has an abnormal mammogram? What about a man with an elevated PSA test, indicating possible prostate cancer? Somehow the 'experts' find it convenient to regard women as hysterical when it comes to ovarian tests."

Sinnex got the attention of her congresswoman, Patsy T. Mink of Hawaii, who introduced three bills calling for more money to be appropriated to ovarian-cancer research at the National Institutes of Health (NIH). Mink's efforts have managed to quadruple the federal funding—from $7 million to $29 million—since her 1990 arrival in Washington. Last year the National Cancer Institute of NIH launched the Prostate, Lung, Colorectal, & Ovarian Cancer (PLCO) Screening Trial. Volunteers at 10 medical centers across the country will be monitored to see if the use of CA 125 and transvaginal sonography will save lives. But this is not the comprehensive study that those concerned with ovarian cancer wanted—for one thing, only women over 60 are included—and there is something of a consensus that the *O* in the PLCO trial was an afterthought, that the inclusion of a female cancer was politically expedient. "I think they had a sense of guilt that they weren't doing very much," says Mink. "We kept pressing them, and they just tacked it on."

"I think it was added inappropriately," says Mount Sinai's Carmel Cohen. "I think the way they're going about it is inadequate, and I think it will give screening a bad name because it will not be successful. But I don't think this is a gender issue. There has been a considerable amount of very brainy effort expended in an attempt to solve the problem of ovarian cancer." Robert Young of the Fox Chase Cancer Center agrees: "Money has never been the source of the debate within the medical community. We do screenings already that aren't cost-effective, but they work. The real hang-up is that we can't just say something is a service without documenting that it is. Everyone who works in this area would love there to be a test."

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In 1993 the American College of Obstetrics and Gynecology stated that "to date, there are insufficient data to recommend any method of screening for ovarian cancer." In April 1994 the NIH Consensus Development Conference on Ovarian Cancer concluded that most women do not need routine screening and risk unnecessary surgery if they insist on testing out of fear. Cohen calls that decision shocking. "The way to avoid the problem is to tighten the indications, not to throw out the technique," he says, and freely recommends transvaginal sonography screening to any woman who can afford it and has access to skilled interpretation of the test (not a so-called imaging center along the lines of X rays 'R Us).

But experienced, respected, caring doctors in the field still disagree about protecting a sister or daughter or wife—or themselves—against ovarian cancer. "I tell them not to get CA 125 or ultrasound," says Beth Karlan. "It leads to a Pandora's box, some of which is driven by a woman's anxiety and medical/legal concerns." She points out that even women with a family history of the disease can reduce their risk *below that of the general population's* by taking oral contraceptives, a confusing bit of information for those who remember when the pill had a bad rap. For all of us, Karlan advises: "Find out your family history—maternal and paternal are equally important—and let your doctor know about it. Get a good pelvic exam, and don't delay if you have symptoms: constant and progressive bloating, wearing sweatsuits because nothing else fits, getting full fast, getting up to pee at night. Most patients feel vaguely bad for about six months. There's a visceral lousiness, but you can't focus on what it is. Although the symptoms are vague, they're present. And if you're with a doctor who blows you off, see someone else."

That "lousiness" alerted Liz Tilberis, who, we are so happy to report, had cutting-edge treatment that appears to have eradicated her disease. Like many ovarian- ➤ 464

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cancer patients, she had chemotherapy with platinum-based drugs—a distant relative of the platinum used in fine jewelry. (Ironically, one of the toxic side effects of chemo is akin to heavy-metal poisoning.) But she was part of a clinical trial in which the standard treatment, spread over six months, was given in just nine weeks, based on studies showing the efficacy of an accelerated program.

Future patients will have even more options, thanks to the cowboys of genetic engineering such as John Mendelsohn, M.D., chief of the department of medicine at the Memorial Sloan-Kettering Cancer Center in NYC, who helped develop an antibody called C-225 that interrupts the growth of cancer cells. "A normal cell has a finite life span and eventually goes down a path called programmed death," explains Samuel Waksal, M.D., president of ImClone Systems, the biopharmaceutical company that funded C-225 research. "When the cell divides, there are genes that are literally stop signs telling it when to stop dividing. What we've learned over the years is that in a cancer cell these 'checkpoint genes' somehow become abnormal, whether because of environmental carcinogens or viruses, and the cell cycle is messed up. A tumor cell does not go down that path. It goes the opposite way in uncontrolled fashion and is 'immortal.'"

Certain types of cancer cells have, on their surface, receptors for growth factors that keep them going. C-225 is a genetically engineered molecule that blocks those receptors and deprives the cells of the juice that makes them grow. "There is a cascade effect," says Waksal. "The cells become incredibly susceptible to chemotherapy, and we're able to drive them to programmed death." In lab experiments, when mice were injected with ovarian-cancer cells and then given conventional ➤

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chemotherapy, the mice died. Same thing when they were treated with C-225. "But if we use chemo plus C-225, there's no tumor growth. The animal is cured every time. It's dramatic."

Here's the catch: "We haven't done it in people yet," says Waksal. "But we understand how this works now, and what we're going to see over the next five years is a dramatic change in therapy for ovarian, breast, and lung cancers. We can begin to find the right molecules to intervene in the cancer-cell cycle. The future is finally now."

For further information, contact the Ovarian Cancer Prevention & Early Detection Foundation, P.O. Box 447, Paauilo, HI 96776-0447. Tel: 808-776-1696 (3:00 P.M–11:00 P.M. EDT). Fax: 808-776-1266.